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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/721,391	11/22/2000	Richard G. Vile	07039-294001	3279

26191 7590 05/05/2004

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/721,391	VILE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004 and 25 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,15,35, 37-43,46-51,53,55-61 and 64-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15, 50-51, 53, 56-61 and 64-67* is/are rejected.

7)☒ Claim(s) *9,35,37-43,46-49 and 55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendments filed on 2/02/04 and 8/25/03 have been entered.

Amended claims 9, 15, 35-43, 46-51, 53, 55-61 and 64-67 are pending in the present application, and they are examined on the merits herein.

Claim Objections

Claim 9 is objected to because the terms "HSE" and "HSF-1" should be spelled out at the first occurrence of the terms. Appropriate correction is required.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 15, 50-51, 53, 56-61 and 64-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is necessitated by Applicants' amendment.**

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v.

Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a composition comprising a nucleic acid, wherein the nucleic acid comprises: (a) a cell type-specific promoter, including **the minimal human tyrosinase promoter** (Tyr300 of SEQ ID NO:1), for activating the expression of a gene in a specific cell type, (b) a therapeutic gene sequence operably linked to said cell type-specific promoter, (c) an amplification promoter element for amplifying transcription of said therapeutic gene in said specific cell type, wherein said amplification promoter element is an HSE; and (d) a sequence encoding a transcription activator, said transcription activator for activating said amplification promoter element, wherein said transcription activator is HSF-1, and **wherein said nucleic acid produces a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type.** The claims encompass a composition comprising a nucleic acid containing **any cell type-specific promoter**, including the minimal human tyrosinase promoter (Tyr300 of SEQ ID NO:1), operably linked to an HSE amplification promoter element and a sequence encoding HSF-1 that activates the HSE amplification promoter element, so that the nucleic acid produces a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type.

However, apart from the exemplification showing the highly tissue-specific heat shock element (HSE)-Tyr-300/heat shock factor–1 (HSF-1) feedback loop system that can be used to kill melanoma cells specifically and efficiently, the instant specification fails to teach a representative number of species of a broad genus of a nucleic acid comprising **any cell-type specific promoter** in combination with the HSE amplification promoter element and a sequence encoding HSF-1 that activates the amplification promoter element, so that the nucleic acid produces a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type. It has been known in the art that tissue-specific promoters are often either **very weak and/or leaky** (Sato et al., Biochem. Biophys. Res. Commun. 244:455-462, 1998, see page 455; Nettelbeck et al., TIG 16:174-181, 2000, see page 175, first full paragraph; Emiliusen et al., Gene therapy 8:987-998, 2001). Apart from the disclosure of **a minimal human tyrosinase promoter** (Tyr300 of SEQ ID NO. 1) which is transcriptionally silent in all of the non-melanoma cells tested, the instant specification fails to describe **any other minimal cell-type specific promoters** that also has the same or similar **strength and specificity** as that of Tyr300, let alone for any cell-type specific promoter, to attain the desired result of getting a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type. It is also well known in the prior art that **high tissue specificity** of a promoter tends to be achieved at the expense of promoter strength. Even in 2001, Emiliusen et al. still state "The format of the feedback loop described here **could be**

exploited for any tissue type in which a highly tissue-specific element can be identified but which is itself too weak to be effective therapeutically" (see abstract, bottom of col. 2), let alone at the effective filing date of the present application (11/23/1999).

The claimed invention as a whole is not adequately described if the claims require essential or critical elements that are not adequately described in the specification. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot fully envision the detailed structure of a broad genus of a nucleic acid comprising any cell type-specific promoter in combination with an HSE amplification promoter element and a sequence encoding HSF-1 that activates the HSE amplification promoter element with the desired property as broadly claimed apart from the disclosed HSE-Tyr-300/HSF-1 feedback loop nucleic acid system, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Response to Arguments

Applicants' arguments related in part to the above rejection in the Amendment filed on 8/25/03 (pages 9-10) have been fully considered, but they are not found persuasive.

Applicants argue basically that the instant specification adequately describes the subject matter of the amended claims. Applicants' specification discloses multiple examples of cell type-specific promoters, including methods for identifying cell type-specific promoters, as well as multiple examples of therapeutic gene sequences, heat shock elements and HSF-1.

Please note that the generic disclosure of cell type-specific promoters such as β-casein promoter, uteroglobin promoter, carboxykinase promoter, tyrosinase promoter, myelin basic promoter and others in the instant specification is not deemed to be sufficient for overcome the written description rejection set forth above. This is because it has been known in the art that tissue-specific promoters are often either **very weak and/or leaky** (Sato et al., Biochem. Biophys. Res. Commun. 244:455-462, 1998, see page 455; Nettelbeck et al., TIG 16:174-181, 2000, see page 175, first full paragraph; Emiliusen et al., Gene therapy 8:987-998, 2001). Due to the **leakiness of tissue-specific promoters known in the art,** then how can an ordinary skilled artisan at the

effective filing date of the present application make a composition with the desired property, producing a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type, as claimed? It is further noted that a minimal human tyrosinase promoter of SEQ ID NO:1 is the **only tyrosinase promoter element** tested or known to be transcriptionally silent in all of the non-melanoma cell lines (see example 1 of the instant specification).

Apart from the disclosure of **a minimal human tyrosinase promoter** (Tyr300 of SEQ ID NO. 1) which is transcriptionally silent in all of the non-melanoma cells tested, the instant specification fails to describe **any other minimal cell-type specific promoters** that also have the same or similar **strength and specificity** as that of Tyr300 to attain the desired result such as producing a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type. What are the structural characteristics of the minimal promoters of β-casein promoter, uteroglobin promoter, carboxykinase promoter or elements of these promoters that are transcriptionally silent in non-specific cell types?

Additionally, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Accordingly, amended claims 15, 50-51, 53, 56-61 and 64-67 are rejected under 35 U.S.C. 112, first paragraph for the reasons set forth above.

Conclusions

Claim 55 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 9 is objected for a minor informality, while claims 35, 37-43 and 46-49 are dependent on the objected claim 9.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER